IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IN RE:	)	
'318 PATENT INFRINGEMENT LITIGATION	)	**Civ. No. 05-356-(SLR) (consolidated)**

DEFENDANTS' JOINT OPENING POST-TRIAL BRIEF

CONFIDENTIAL: FILED UNDER SEAL
SUBJECT TO A PROTECTIVE ORDER

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I. SUMMARY OF ARGUMENT

The '318 patent's disclosure is nothing more than a two page summary of six prior art references concerning galanthamine coupled with the suggestion that someone do animal testing to determine whether galanthamine can be used to treat Alzheimer's Disease ("AD"). The inventor, Dr. Bonnie Davis, literally disclosed nothing in her patent specification that had not appeared previously in the prior art: she did no testing with galanthamine and disclosed no new theories concerning the treatment of AD. She essentially said that someone ought to try galanthamine as a treatment for AD. Patents are "a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention for a period of years." *Bonito Boats v. Thunder Craft Boats*, 489 U.S. 141, 149 (1989). Dr. Davis did not meet her end of the bargain.

Faced with the patent's slight disclosure on the one hand, and the Supreme Court's "lowered bar" for obviousness as recently set forth in *KSR* on the other, Plaintiffs can avoid conceding invalidity only by asserting diametrically opposed positions as to the prior art depending on what defense they are discussing. When responding to Defendants' obviousness and anticipation defenses, Plaintiffs strenuously argue that the prior art provided absolutely *no* reason for one of ordinary skill to even think of galanthamine as a potential AD treatment. When responding to Defendants' enablement defense, Plaintiffs say the exact opposite, presenting at trial a theory that the prior art references in the patent demonstrate that galanthamine, without question, *would* work as a treatment for AD. Plaintiffs simply cannot have it both ways.

Defendants consistently have maintained that the purported invention is obvious and anticipated in light of the prior art. This is precisely the type of combination of elements case addressed by *KSR*. Both elements of the claimed invention were well known in the art: that

cognitive problems in AD patients could be treated with cholinesterase inhibitors ("CIs") and that galanthamine was a CI that had superior properties for administration to humans. Galanthamine perfectly fit the need identified in the prior art for a CI with a better therapeutic profile than the CIs that had been used to treat AD prior to 1986. Under *KSR*, the predictable result of the combination of these two known elements renders the patent obvious. In fact, the *Bhasker* article, written long before the patent application was filed, specifically suggested that galanthamine could be used to treat progressive dementias, which would have been understood to include AD. As such, the patent is invalid as anticipated by the teachings in *Bhasker*.

But if, as Plaintiffs' experts assert, Defendants are wrong and there was no reasonable expectation that galanthamine would work for its intended purpose, then the lack of a meaningful disclosure utterly fails to enable the patent. Enablement requires that the patent provide evidence substantiating the utility of the drug or that those of ordinary skill accept that utility "without question." The patent's specification literally provides no information on the utility of galanthamine as an AD treatment, leaving only the prior art to provide a basis for enablement. If, as Plaintiffs' experts say, the prior art provides no reason to believe that galanthamine would work as a treatment for AD, the patent cannot be enabled.

In short, the prior art is what it is and does not change just because a different defense is asserted. The patent either makes no innovative contribution to the art and is obvious, or it provides one of ordinary skill in the art with no evidence of utility and is not enabled. Thus, the '318 patent is invalid and judgment should be entered in favor of the Defendants.

II. STATEMENT OF FACTS

Dr. Davis filed her patent application for United States Patent No. 4,663,318 ("the '318 patent") on January 15, 1986. PX 1. The patent issued on May 5, 1987. *Id.* Claim 1 claims a method of treating AD and related dementias by administering a therapeutically effective amount

of galanthamine to patients. *Id.* Claim 4 depends from claim 1 and adds the limitation that galanthamine should be administered orally in the dosage range of 10-2000 mg. *Id.*

A. Facts Compelling A Finding That The '318 Patent Is Anticipated And/Or Obvious In Light Of The Prior Art

1. Scope and Content of the Prior Art

a. Alzheimer's Disease

AD was discovered by Dr. Alois Alzheimer in approximately 1906 in a 51-year old female patient "who developed memory loss and paranoia." Levey[1] 95:5-25. Upon autopsy of her brain, Dr. Alzheimer described what are today the classic "pathological hallmarks of the disease" — neurofibrillary tangles and plaques. Levey 95:15-17. While AD was initially viewed as a form of pre-senile dementia, a person of ordinary skill in the art, by 1986, would have understood that AD encompassed both the pre-senile and senile forms of dementia.[2] Levey 95:18-97:3.

By 1986, AD was recognized as the most common form of dementia. Levey 321:4-7; PX 752 at 1 (Rathmann, 1984). AD was recognized as a progressive dementia that destroys higher cortical functions, including memory, judgment, reasoning, and language ability. Levey 100:2-10, 186:12-14, 213:2-4; PX 752 at 685 (Rathmann, 1984). AD "almost always begins with insidious onset of the memory problems, which progress over time to develop into more serious memory problems, and then begin[s] to affect other higher brain functions, such as judgment and reasoning, such as language ability, such as perception and recognition." Levey 100:1-10. Those "are the cognitive aspects of the disease." Levey 100:9-10. In addition to the cognitive

[1] Citations to the trial transcript appear as follows: witness name page:line.

[2] This does not alter Defendants' claim construction position regarding Claim 1's use of the term "Alzheimer's disease and related dementias." In her patent, Dr. Davis, as her own lexicographer, defined AD to be pre-senile dementia. Thus, related dementias means dementias (plural) related to AD, not just senile dementia of the Alzheimer's type. *See* Defendants' claim construction briefs, DI 323 and DI 341.

aspects of the disease, it was well-known "that the disease also affects behavioral problems." Levey 100:11-12. By 1986, it also was known that the course of AD can be variable. Levey 100:20-101:4; Coyle 992:16-21; PX 752 at 685 (Rathmann, 1984). Some patients, particularly those with pre-senile dementia, progress rapidly downhill in a matter of one or two years. Levey 101:1-4; PX 752 at 685 (Rathmann, 1984). Others suffer from the disease for up to twenty years. Levey 101:1-4.

b. The Cholinergic Prior Art

i. *Acetylcholine is decreased in AD*

From the time of the discovery of AD until the early 1970s, very little was known about its possible causes. Levey 118:12-24. That changed in the mid to late 1970s when researchers associated decreases in acetylcholine levels in the brain with diminished memory and cognitive functions in normal patients. Levey 110:7-11, 117:22-25; DX 495 at 113-121 (Drachmann, 1974). This led researchers to study whether diminished acetylcholine levels were implicated in AD. Levey 118:13-24; DX 167 at 1457-1459 (Perry, 1978). Several prominent AD research groups determined in autopsies of AD patients that the chemical marker for acetylcholine was markedly decreased in their brains and the extent of the decrease correlated with the number of plaques and tangles present in the brain and the degree of intellectual impairment. *See* Levey 124:14-24; DX 167 at 1457-1459 (Perry, 1978); DX 139 at 1403 (Davies, 1976). The discovery that acetylcholine was decreased in AD patients was monumental for AD research because it provided a scientifically-grounded reason to believe that a reduction in acetylcholine was responsible for at least some of the actual "clinical symptoms of the disease," such as loss of memory. Levey 124:25-127:12; Domino 382:9-383:15.

The discovery that acetylcholine was decreased in brains of AD patients led to the hypothesis that if you could address that deficit, you could treat AD. Levey 127:1-20. This

became known as the "cholinergic hypothesis,"[3] (Levey 126:24-127:13) and by 1986, there was a large body of evidence supporting it. Domino 382:9-383:15; Raskind 1227:19-1228:6. Studies were published in some of the most respected medical and science journals in the world, such as *Science, JAMA, The New England Journal of Medicine* and *The Lancet*. *See* PX 663 at 1184-89 (Coyle, 1983); DX 139 at 1403 (Davies, 1976); PX 1205 at 720-21 (Thal, 1983); DX 1233 (Timeline of Prior Art). Plaintiffs' expert, Dr. Coyle, stated in his *Science* article 1983, that the "evidence available to date suggests that this transmitter system [the cholinergic system] is involved most consistently and most severely in AD." PX 663 at 1188 (Coyle, 1983). Consequently, the "identified cholinergic lesion in AD has important implications for its diagnosis, treatment, and ultimately its prevention." *Id.*

By 1986, the "primary emphasis in [the] treatment of [AD] [was] directed at enhancing cholinergic activity." PX 752 at 684 (Rathmann, 1984); Levey 127:25-128:3, 167:4-168:1. The cholinergic deficit hypothesis "really distinguished itself [from other treatment approaches] because there was such solid scientific evidence." Levey 167:11-18. Dr. Raskind, Plaintiffs' expert agreed: "there was a large body of evidence . . . surrounding the cholinergic hypothesis and the deficits that are seen in the disease . . ." Raskind 1227:19-22. The cholinergic deficit hypothesis "was really guiding therapy" for AD by 1986. Levey 167:13-24. In fact, by 1986, the cholinergic deficit hypothesis was the AD treatment approach with the largest body of scientific evidence supporting it. *See* Domino 436:22-442:13; *see also* Levey 167:13-19.

By 1986, there were no less than 15 prior art references discussing the research efforts that were underway to treat AD based on the cholinergic deficit hypothesis. PX 19 at 330-36 (Kendall, 1985); PX 213 (Drachman, 1984); PX 632 (Bartus, 1985); PX 653 (Bartus, 1982); PX

[3]The term "cholinergic hypothesis" and "cholinergic deficit hypothesis" mean the same thing and are used interchangeably herein. Levey 128:4-9. The cholinergic system "refers to the group of brain cells that actually use acetylcholine as a chemical messenger." Levey 101:18-23.

670 (K. Davis 1983); PX 698 (Mohs, 1985); PX 699 (Mohs, 1985); PX 711 (Summers, 1981), PX 719 (Wurtman, 1984); PX 727 (C. Johns, 1983); PX 752 (Rathmann, 1984); PX 763 (K. Davis, 1982); PX 1148 (Greenwald, 1983); PX 1200 (Smith, 1979); PX 1205 (Thal, 1983).

ii. *Treatment Approaches Based on the Cholinergic Deficit Hypothesis*

Scientists developed treatment approaches to AD that focused on correcting the acetylcholine deficit. Levey 128:13-130:25; *see* PX 752 (Rathmann, 1984). In particular, scientists pursued three different approaches: pre-synaptic, intra-synaptic and post-synaptic. Levey 128:13-130:25; PX 19 at 329 (Kendall, 1985); DX 1200.

Of the three approaches, the intra-synaptic (or CI) approach consistently produced the greatest improvement in cognitive function in AD patients. *See* Levey 129:19-130:22; Domino 382:9-383:15; *see, e.g.,* PX 727 at 185-193 (C. Johns, 1983); PX 752 at 668 (Rathmann, 1984). The logic behind the CI approach was to block the activity of an enzyme called acetylcholinesterase ("AchE"). Levey 130:16-18. AchE breaks down acetylcholine in the brain and as a result, causes a deficiency of acetylcholine in AD patients. DX 167 at 1457-59 (Perry, 1978); DX 139 at 1403 (Davies, 1976); Levey 105:8-14, 124:14-127:12. Reversible tertiary CIs are drugs that enter the brain and stop AchE from breaking down acetylcholine. Levey 107:13-108:10, 178:5-24; PX 752 at 688 (Rathmann, 1984). The logic behind the use of CIs was to increase the amount of acetylcholine in the brain and thereby improve cognitive function in AD patients. *See* PX 763 at 1421 (K. Davis, 1982); Levey 130:16-18, 135:3-136:10.[4]

[4] As Dr. Levey testified, neither the pre-synaptic nor the post-synaptic approach generated the type of consistently replicated positive results that were seen with the CI approach. Levey 129:19-130:10. For example, Plaintiffs' expert Dr. Coyle testified that by 1986 "people were disappointed with the precursor studies" [pre-synaptic approach] because they did not reveal any consistently positive results. Coyle 865:16-19. Likewise, prior art relied on by Plaintiffs reported that the agonist approach [post-synaptic approach] was uncertain because "the pharmacological studies supporting the superiority of the cholinergic agonists remain[ed] sparse and tentative and require[ed] additional tests and comparisons." PX 632 at 342 (Bartus, 1985).

As of 1986, the CIs used in humans in the United States were physostigmine and tacrine. Levey 230:6-15; PX 711 (Summers, 1981); PX 698 (Mohs, 1985); PX 699 (Mohs, 1985). Physostigmine and tacrine were known as reversible tertiary CIs, which meant that they could enter the brain, inhibit AchE, and increase the levels of acetylcholine in the brains of AD patients. Levey 178:6-179:2; Domino 382:9-383:7; 386:2-21; *see also,* DX 58 (Cozanitis, 1974); DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977); PX 711 (Summers, 1981). By January 1986, at least 14 prior art references reported that doses of physostigmine and/or tacrine improved cognitive function in AD patients, and that the effects could be "clinically significant." Levey, 230:6-13; *see, e.g.* PX 19 at 330 (Kendall, 1985); PX 632 at 341-42 (Bartus, 1985); PX 653 at 413 (Bartus, 1982); PX 663 at 1188 (Coyle, 1983); PX 670 (K. Davis, 1983); PX 698 (Mohs, 1985); PX 699 (Mohs, 1985); PX 711 (Summers, 1981); PX 727 (C. Johns, 1983); PX 752 (Rathmann, 1984); PX 763 (K. Davis, 1982); PX 1148 (Greenwald, 1983); PX 1200 (Smith, 1979); PX 1205 (Thal, 1979); DX 1233 (Timeline of prior art). For instance, the following reported:

- Smith, C.M., et al., "Physostigmine in AD," The Lancet I: 42 (January 6, 1979) (PX 1200 at 42).
    - In a pilot study with one AD patient, the authors reported a reduction in intrusion errors observed after physostigmine was given. *Id.* at 42; Levey 133:1-18 ("with physostigmine they could measure some improvement.")
- Thal, *et al.* "Memory Enhancement with Oral Physostigmine in Alzheimer's Disease," New England Journal of Medicine, 308(12):720-1 (1983) (PX 1205).
    - Reported that 8 of the 12 AD patients showed improvement in memory after receiving intravenous physostigmine and the results were replicated. *Id.*; Levey 142:7-145:25.
- Davis K.L., and Mohs, R., "Enhancement of Memory Processes in AD with Multiple Dose Intravenous Physostigmine," American Journal of Psychiatry

Vol. 139, No. 11, pp. 1421-1424 (1982) (PX 763 at 1422); Levey 135:3-136:10.

- Reported that 9 of the 10 AD patients showed memory improvement after being given physostigmine. During the replication phase, 8 of the 10 demonstrated a physostigmine related improvement in long-term memory. *Id.* at 1422.

- K.L. Davis, *et al.*, "Oral Physostigmine in Alzheimer's Disease," Psychopharmacology Bull., Vol. 19 No. 3 451-453 (1983) (PX 670 at 451); Raskind 1247:15-1248:3; Raskind 1248:11-1249:20.

  - Reported that the "dose-finding phase of the study elicited a dose of physostigmine that lowered the ADAS [cognitive test] (improved performance) in eight of the nine patients." Upon replication all but two of these patients improved after being given physostigmine. *Id.* at 451. In 2 patients, the effects were clinically meaningful and the families actively encouraged treatment. *Id.* at 452.

- K.L. Davis, *et al.*, "The Cholinergic Treatment Strategy in Aging and Senile Dementia," Psychopharmacology Bull., Vol. 19 No. 2 pp. 185-197 (PX 727 at 189-193); Levey 160:23-164:25.

  - In a review of pre-1983 physostigmine and tacrine studies, Ken Davis, *et al.* reported that "[o]f the seven studies of parenteral physostigmine in SDAT . . . five . . . demonstrated mild to moderate transient improvements during physostigmine administration." *Id.* at 190-91.

  - The authors explained that the "apparently contradictory nature of some [pre-1983] findings may be explained and reconciled" due to the use of testing that was too nuanced to track improvement, inaccurate dosing, or the inclusion of patients whose AD was too severe for any cholinergic drug to have an effect. *Id.* at 189-193.

- Mohs, R.C., *et al.* "Clinical Studies of the Cholinergic Deficit in Alzheimer's Disease," Journal of American Geriatrics Society, Vol. 33 pp. 749-757 (1985) (PX 698 at 749).

  - Reported that intravenous physostigmine significantly and reliably enhanced memory in 13 of the 16 AD patients tested. Oral physostigmine was reported to reliably decrease overall symptom severity in 7 of the 12 AD patients tested. *Id.* at 749.

- Mohs, R.C., et al., "Oral Physostigmine Treatment of Patients with AD," Am. J. Psychiat., Vol. 142 pp. 28-33, (1985) (PX 699 at 28).

- "Of the 10 patients who completed the study, three showed clinically significant improvement on the highest physostigmine dose in both phases, four more were marginally improved in both phases, and three had inconsistent responses to physostigmine." *Id.* at 28; Levey 150:17-151:14.

- Summers, W.K., et al., "Use of THA in Treatment of Alzheimer-Like Dementia: Pilot Study in 12 Patients," Biological Psychiatry, Vol. 16, pp. 145-153 (1981) (PX 711 at 145).

  - "THA [tacrine], a centrally acting anticholinesterase, was given intravenously in varying doses to 12 unselected cases of Alzheimer-like senile dementia. Significant improvement in memory testing occurred in 6 of 12 subjects; 9 of 12 improved in clinical staging." *Id.* at 1145; Levey 157:10-25 ("there's a subset of patients who responded . . . clinically meaningfully to the drugs").

Numerous review articles also were written to summarize and assess the studies with CIs, demonstrating the preeminence and promise of the approach. Levey 159:1-19. As with the individual studies, the review articles acknowledged that CIs produced beneficial effects in some patients and further research should be conducted. *See, e.g.*, PX 19 (Kendall, 1985); PX 631 (Hollister, 1984); PX 632 (Bartus, 1985); PX 752 (Rathmann, 1984); PX 727 (C. Johns, 1983); PX 1148 (Greenwald, 1983).

While physostigmine and tacrine were shown to be effective agents for improvement of cognitive function in AD patients (*i.e.*, a method of treating AD), the drugs themselves had characteristics that limited their clinical usefulness. Levey 173:13-174:20. In particular, "[p]hysostigmine's clinical usefulness [was] limited, however, due to peripheral side effects and its short duration of action." Levey 169:7-171:1; *see also* PX 752 at 688 (Rathmann, 1984).[5] In the case of physostigmine, depending on whether the drug was given orally or intravenously, the duration of action was reported "as less than 1 hour" or "30 to 60 minutes." Levey 170:11-21;

[5] Peripheral side effects refer to the fact that physostigmine caused people to "get sick to their stomach" or "sweat profusely." Levey 169:7-171:1. Short duration of action referred to the relatively short period of time that physostigmine was active in the human body. Levey 170:7-21.

PX 752 at 688 (Rathmann, 1984). Accordingly, physostigmine's clinical usefulness was limited because it had to be administered very frequently to AD patients. *Id.* Prior to 1986, tacrine was described as having more potential than physostigmine because it "ha[d] a longer life than oral physostigmine and ha[d] fewer peripheral side effects . . ."[6] PX 727 at 192 (C. Johns, 1983).

As Dr. Levey testified, the 1985 Rathmann review accurately captured the state of the art for cholinergic treatment approaches to AD as of 1986. Levey 224:5-10. Rathmann disclosed:

- "Neurochemical studies suggest a cholinergic deficit; thus primary emphasis in treatment has been directed at enhancing cholinergic activity." PX 752 at 684 (Rathmann, 1984); Levey 167:8-25.

- "Results with physostigmine are encouraging and further studies with this drug prototype are needed." *Id.*; Levey 168:19-169:5.

- "Physostigmine's clinical usefulness is limited, however, due to peripheral side effects and its short duration of action." *Id.* at 684. Nonetheless, "it has served as a useful pharmacological model." *Id.* at 688; Levey 169:7-171:1, 173:13-174:25.

Other review articles of the time, prior to 1986, reported similar findings:

- C. Johns, *et al.* review concluded that "trials of pharmacologic agents that enhance cholinergic activity should be aggressively pursued, as they offer a rational treatment strategy based on observed neurochemical deficits." PX 727 at 193 (C. Johns, 1983).

- The Kendall review reported that "[p]hysostigmine does penetrate into the central nervous system and early trials with this drug have yielded some encouraging results . . . physostigmine . . . has been shown to produce an improvement . . . in patients with [AD]." PX 19 at 329-330 (Kendall, 1985).

- The Hollister review disclosed that "[r]ecently, reports of success with acetylcholinesterase inhibitors, such as physostigmine, have aroused considerable interest (11)." PX 631 at 303 (Hollister, 1984).

- The Greenwald, *et al.* review reported "in AD patients, physostigmine has been reported to improve praxis and decrease the number of intrusion errors on recall tasks." PX 1148 at 313 (Greenwald, 1983). Additionally the authors reported

[6] After 1986, however, tacrine was reported to cause elevated liver enzymes levels in AD patients. Coyle 838:17-839:19.

that "Tetrahydroaminoacridine (THA) a longer-acting acetylcholinesterase inhibitor, has produced global improvements in AD patients." *Id.*

- Bartus' review also reported that "[i]t is now generally accepted that physostigmine can improve geriatric memory" and that "the available studies with cholinergic agents provide the optimist with a basis of hope for future drug development." PX 632 at 341, 343 (Bartus, 1985).

Once it was known that physostigmine and tacrine improved cognitive function in AD patients, it was logical to look for other tertiary CIs that overcame their limitations. Domino 388:17-394:7; Levey 173:13-175:13. As Plaintiffs' expert Dr. Raskind testified, in drug development, "drugs tend often to be derivative. You need some pointers that will show you the way and if you have something that works, then you can logically work forward from there to develop, hopefully, yet better compounds that will work more effectively." Raskind 1089:24-1090:3. The repeated findings that physostigmine and tacrine improved cognitive function in AD patients would have motivated scientists to "go full speed ahead" by pursuing other tertiary CIs that were longer-acting and had less peripheral side-effects than physostigmine. *See* PX 727 at 193 (C. Johns, 1983); PX 1148 (Greenwald, 1983); PX 752 at 688 (Rathmann, 1984); Levey 227:4-231:13; Domino 388:17-394:7, 391:13-15 ("go full speed ahead to find another member in the family of reversible [CIs] that penetrate the blood/brain barrier").

iii. *Galanthamine Prior Art*

Galanthamine fit the criteria for the next generation of reversible tertiary amine CIs perfectly. Levey 204:8-205:23; Domino 393:1-397:24. In fact, Dr. Davis said the prior art was "virtually a prescription for galanthamine." B. Davis 789:5-791:16.

She was right. By 1986, a person of ordinary skill in the art would have known from the extensive prior art that galanthamine was in the same class as physostigmine and tacrine: it was a reversible tertiary CI. *See* DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977); PX 743 (Daskalov, 1980); PX 744 (Luria, 1969); PX 1181 (Pernov, 1961); Levey 178:6-180:17. The fact that

galanthamine was a known "tertiary amine" CI meant that it had the necessary "chemical structure" to "penetrate into the brain" and "inhibit [AchE] in the brain." Levey 178:6-13. It also was well known that galanthamine reversed scopolamine-induced amnesia, which was an early model of AD. DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977); Levey 193:3-200:24; 256:7-12; B. Davis 694:24-695:1 ("[u]p until '83, '84, the predominant model [for AD] was scopolamine . . .").

Cozanitis' and Baraka's 1977 articles disclosed that galanthamine could reverse a scopolamine-induced central cholinergic deficit. DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977). In fact, both the Cozanitis and Baraka articles disclosed that galanthamine had "certain advantages over physostigmine" because it was tolerated in humans, longer-acting than physostigmine (DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977)), "rapidly crossed the blood-brain barrier" (DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977)), and was "hydrolysis-resistant," unlike physostigmine, which meant that it would not be broken down as quickly as physostigmine, which in turn, resulted in its longer duration of action. DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977). The authors concluded that galanthamine could be "used clinically to produce an effective and long-lasting reversal" of scopolamine's central anticholinergic effects in the brain. DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977); Levey 193:3-200:24.

Additionally, by 1986, it was known that galanthamine could be used clinically and safely to restore higher cortical functions that are disturbed in AD patients by inhibiting AchE activity in the brain. PX 744 at 375-400 (Luria, 1969); DX 483 (Bhasker, 1974); PX 1181 (Pernov, 1961); Levey 184:14-190:4; 206:5-220:6; Domino 488:21-489:3. Dr. Luria, "one of the pioneers" in the area of cognitive neurology, discussed how to restore higher cortical functions in the case of local brain damage in particular functions that are also affected by AD: "language

functions, memory functions, sensory perception . . . reasoning." Levey 185:7-186:14. Luria taught that "galanthamine has been used in lots of patients, that it's used safely, that it gets into the brain, that it's able to actually improve higher cortical functions or higher brain functions, including the same types of functions that are impaired in [AD]." Levey 189:24-190:3. Luria also disclosed that "galanthamine is tolerated better than [physostigmine] and possesses a more marked and lasting effect when given for the deinhibition of motor and sensory functions." Levey 191:7-192:20. As Dr. Levey testified, again without contradiction by Plaintiffs, a person of skill in the art would understand that galanthamine's "potency or efficacy was better . . . and it has a . . . longer duration of action." *Id.* Indeed, Bhasker's 1974 article disclosed the treatment of dementias like AD with galanthamine. DX 483 (Bhasker, 1974).

Moreover, the prior art disclosed the dosage ranges of galanthamine that produced clinically significant improvement in patients with higher cortical function abnormalities similar to those seen in AD. PX 743 (Daskalov, 1980). Additionally, in the Daskalov reference, which Dr. Levey testified accurately captures the state of the art as of 1986 with respect to galanthamine, it was reported that dosages between 3 to 20 mg of galanthamine, a centrally-acting CI, had the ability to improve aphasia, one of the symptoms of AD, in 16 out of 23 patients after a stroke. Levey 202:9-204:24.

Thus, by 1986, a person of ordinary skill in the art would have known, *inter alia,* that, compared to physostigmine, galanthamine was longer acting, much less toxic, and had been used safely in clinical practice for a wide variety of disorders, both central and peripheral, without causing adverse side-effects. *See* DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977); DX 483 (Bhasker, 1974); PX 1181 (Pernov, 1961); Levey 181:8-184:2; 193:3-197:17; 200:8-24; Domino 406:18-407:25. Accordingly, each of the criteria set forth by the prior art for an improved CI

was met by galanthamine.[7] As of 1986, the evidence is overwhelming that all limitations of claims 1 and 4 of the '318 patent were in the prior art and the patent does nothing more than combine these known elements in a predictable way.

B. Facts Compelling A Finding That The '318 Patent Is Not Enabled

The '318 patent is only two columns long. PX 1. Those two columns do nothing more than cite six articles that had long been in the prior art. *Id*; col. 1 lines 11-33. In addition, the '318 patent discloses a known animal model, but fails to disclose results from testing with galanthamine in this animal model. B. Davis 824:10-825:18. The inventor admitted that the patent provides no experimental data supporting galanthamine's utility as a treatment for AD, because she did no testing. *Id.* In essence, there was nothing new on the face of the patent demonstrating that galanthamine would work as a treatment for AD. B. Davis 824:10-825:6.

III. ARGUMENT

A. Claim Construction

The parties submitted opening claim construction briefs on December 4, 2006 (DI 322 and DI 323) and responsive briefs on December 20, 2006 (DI 340 and DI 341) and heard argument about claim construction at the pre-trial hearing on April 18, 2007. In essence there are only two terms of Claim 1 in dispute: "Alzheimer's disease and related dementias" and a "method of treating."[8] While Defendants believe that the patent is invalid whatever construction the Court gives, Defendants believe that their constructions on both terms are correct and Plaintiffs provided no evidence at trial otherwise.

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[7] The testimony at trial supports the conclusion that the Eastern European developed drug galanthamine was not used in the U.S. due to administrative, rather than scientific, hurdles. Dr. Ken Davis testified that he was not willing to use galanthamine in his studies because "there was no way we could get an IND from the FDA for this drug." K. Davis 1043:8-10.

[8] Construction of the term "a therapeutically effective amount" is tied to the construction of "method of treating."

Defendants stated in their *Markman* briefs that "Alzheimer's disease and related dementias" means pre-senile dementia and dementias related to AD. *See* DI 323 at 1-6. Plaintiffs believe that the term "related dementias" means only senile dementia of the Alzheimer type. Setting aside the fact that this inappropriately converts the plural "dementias" into the singular "dementia," both parties' experts identified dementias beyond senile dementia of the Alzheimer's type that are related to AD. Levey 318:6-14; Coyle 859:25-860:4. Thus, only Defendants' construction of "related dementias" is supported by the evidence and common sense. [9]Regarding the proper construction for "method of treating," Defendants believe that this means administering galanthamine to improve the cognitive function or functional status of an AD patient. *See* DI 323 at 8-15. This simply means that the drug has to work. *Id.* Plaintiffs attempt to incorporate clinical, safety, and tolerability requirements, things that may be important to the FDA, but are nowhere discussed in the patent.

B. Bhasker Anticipates The Invention Disclosed In Claim 1 Of The '318 Patent

Plaintiffs' claim that no one would ever have thought to use galanthamine as a treatment for AD is definitively disproved by the 1974 Bhasker article, which specifically discloses all elements of the claimed invention. A patent claim is invalid for anticipation if "the invention was patented or described in a printed publication in this or a foreign country ... more than one year prior to the date of the application for the patent in the United States." 35 U.S.C. § 102(b). Anticipation is established if every element of a properly construed claim is present in a single prior art reference. *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005). Bhasker contains every element of Claim 1 of the '318 patent and therefore renders it invalid.

[9] Beyond the lack of enablement regarding galanthamine as set forth *infra*, Dr. Davis certainly did not enable a person of ordinary skill in the art to use galanthamine to treat these related dementias and is yet another reason why the patent is invalid.

1. Bhasker Discloses All Elements Of Claim 1

Bhasker's article, "Medical Management of Dementia," was published in the journal The Antiseptic Vol. 71 No. 1 in 1974 ("Bhasker"). Generally, the article discusses techniques for managing dementia patients. Specifically, the article discloses the use of galanthamine as a treatment for irreversible progressive dementias like AD.

In the first four paragraphs of the article, Bhasker sets forth three categories of dementia: reversible dementias (dementias where one can find the cause and "reverse" the dementia, Levey 208:20-209:13), arrested dementias (where "the cause of the dementia can be identified and corrected, but the dementia will not itself get significantly better," Levey 209:18-21), and irreversible or progressive dementias ("where there is a progressive fall-out of neurons and the course of the illness is rapidly downhill." DX 483). One of skill in the art in 1986 would have understood AD to be an irreversible/ progressive dementia. Levey 213:2-9; Domino 488:14-17.

Bhasker then discusses management of the class of progressive dementias. The fifth paragraph notes that "[o]nly management and no treatment is possible." DX 483-01. Subsequent paragraphs discuss various ways of managing progressive dementia, including using drugs to control involuntary movements (¶6), using other drugs and psychiatric care to deal with behavior problems of dementia patients (¶7), and carefully supervising and providing nursing care regarding nutritional and personal cleanliness (¶8). DX 483-02; Levey 213:10-215:9.

In the 9th paragraph, Bhasker turns to possible treatments of progressive dementias: "The restoration of higher cortical functions is difficult and was once considered impossible; but it has lately gained importance." DX 483; Levey 216:2-10. One of ordinary skill would understand that "[h]igher cortical functions" refers to cognitive functions, such as memory, which are implicated in AD. Levey 186:3-14. Bhasker recognized that it was once considered

impossible to restore those functions, which would be a treatment of the progressive dementia, but noted that "lately" such approaches were gaining considerable importance. *Id.* 217:3-11.

Then Bhasker specifically discussed galanthamine and its prior use in restoring higher cortical function:

> *The restoration of higher cortical functions is difficult and was once considered to [be] impossible; but it has lately gained importance.* Luria and his colleagues have dealt with this problem in great detail. They have suggested measures of improving the higher functions in cases of local brain damage like tumour, head injury, infarct etc., by deinhibitory procedures and re-education of the rest of the brain. *Deinhibition refers to the facilitation of acetylcholine activity by giving small daily doses of Cholinesterase inhibitors (Neostigmine, Gallanthamine etc.).*

DX 483-02(emphasis added); Levey 218:25-219:13.[10] Therefore, Bhasker relies on the knowledge in the art that acetylcholine activity is tied to cognitive function in dementia patients and suggests that by improving acetylcholine activity galanthamine can help to restore higher cortical function in patients suffering from progressive dementias like AD.[11]

As Dr. Levey testified, Bhasker anticipates all of the limitations of Claim 1 of the '318 patent (220:24-221:2; 223:3-7):

- Bhasker discloses treatment of patients with progressive dementia, which includes AD. 221:24-222:5.
- Bhasker discloses the administration to a patient of a small amount of galanthamine. 222:6-12.
- Bhasker discloses the administration of a therapeutically effective amount of galanthamine by referring to amounts sufficient to improve higher cortical function. 222:13-22.

[10] Deinhibition refers to the mechanism of action of a CI. It prevents or inhibits AchE from breaking down acetylcholine thus facilitating acetylcholine activity. *See* DX 1200; Domino 402:24-403:10.

[11] Luria was "a very famous brain researcher," who was "one of the pioneers under cognitive neurology in a sense, understanding higher brain functions," and is "one of the most respected people in the field." One of ordinary skill in the art in 1986 would have known of Luria and his work, as both party's experts testified. Levey 184:6-185:13; 191:7-20; 217:12-218:13; Coyle 991:15-992:5.

- Bhasker inherently discloses what that amount would be because one of ordinary skill in the art in 1986 would have known what a therapeutically effective amount of galanthamine would be. 222:23-223:2.

Bhasker, writing years before Dr. Davis filed her patent application, discloses all elements of and therefore anticipates Claim 1 of the '318 patent.

2. Plaintiffs' Arguments Against Anticipation Fail

Plaintiffs' arguments concerning Bhasker are inconsequential. First, Plaintiffs argue that Bhasker does not specifically use the term "Alzheimer's disease." Coyle 935:14-24. It is black letter law that an anticipating reference need not use the exact words of the claim. *See, e.g., Novo Nordisk Pharms., Inc. v. Bio-Tech. Gen. Corp.*, 2004 U.S. Dist. Lexis 14960, at * 71 (D. Del. 2004) (A reference "need not be *ipsissimis verbis* (*i.e.*, use identical words as those recited in the claims) to be expressly anticipating."). Bhasker specifically references progressive or irreversible dementias. In 1986, one of skill in the art clearly would have understood that AD was a progressive or irreversible dementia. Coyle 990:9-991:2. Nothing more is required.

Second, Plaintiffs claim that Bhasker's statement that "only management and no treatment is available" means that Bhasker was not suggesting galanthamine as a treatment for progressive dementias like AD. Coyle 935:14-936:5. Plaintiffs, however, ignore Bhasker's later comment that while treatments of progressive dementia had failed in the past, they "had lately gained in importance." The clear message is that "there's hope on the horizon" for the restoration of higher cortical function, which clearly is a treatment, not management of progressive dementia. *See* Domino 488:21-489:3. As Dr. Levey stated: "at this part of the article he's ... talking about ... treatment possibilities." 216:8-10.

Third, Plaintiffs argue that Bhasker's reference to neostigmine, a drug that in most circumstances cannot be used to treat AD, indicates that the sentence is not intended to address treatments of AD. Plaintiffs ignore the context. The sentence appears in a paragraph devoted to

restoration of higher cortical function in patients suffering from progressive dementia. Bhasker's reference to galanthamine makes clear that it is a drug that can restore higher cortical function in that context. Moreover, one of ordinary skill in the art would have known that galanthamine could cross the blood brain barrier and therefore could serve as a treatment for AD, even if neostigmine could not. *Helifix Ltd. v. Blok-Lok, Ltd.*, 208 F.3d 1339, 1347 (Fed. Cir. 2000); *In re Graves*, 69 F.3d 1147, 1152 (Fed. Cir. 1995).[12]

Finally, Plaintiffs desperately argue that Bhasker is not a printed publication. Under § 102(b), a reference need only be publicly accessible. *See, e.g., SRI Int'l Inc. v. Internet Sec. Sys., Inc.*, 456 F. Supp. 2d 623, 628 (D. Del. 2006). As the court in *American Stock Exchange, LLC v. Mopex, Inc.*, observed:

> ***Surely, if a single copy of a doctoral dissertation maintained in one university library in Germany has been found to be "publicly accessible,"*** *see In re Hall*, 781 F.2d at 899-900, so too is an application that is indexed in the Reference Room – the most logical place to look for prior art.

250 F. Supp. 2d 323, 329 (S.D.N.Y. 2003)(emphasis added).

Bhasker was indexed in 1975 in Excerpta Medica and was publicly available in at least the University of Michigan Medical Library prior to January 15, 1986. Domino 403:13-405:7; DX 74. One skilled in the art could have located the Bhasker article by searching for it in the index, just as Dr. Domino actually did. Domino 405:21-406:17. Dr. Coyle's testimony that he did not personally see Bhasker is irrelevant (Coyle 934:11-13), particularly in light of his admission that Bhasker was publicly available. *Id.* 987:12-16; 989:24-990:3. As such, there is no dispute that Bhasker is a printed publication under § 102(b).

[12] At trial, it was unclear whether Plaintiffs were contending that one of ordinary skill would have viewed Bhasker as teaching away from Claim 1 of the '318 patent. However, even if they were, whether through Bhasker's reference to neostigmine or his statement regarding "no treatment," that has no bearing on the anticipatory nature ot the content disclosed in Bhasker. "A reference is no less anticipatory if, after disclosing the invention, the reference then disparages it. Thus, the question whether a reference 'teaches away' from the invention is inapplicable to an anticipation analysis." *Celeritas Techs. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998).

3. Plaintiffs Failed to Prove Bhasker Was Not Enabled

As this Court has stated, the "patentee bears the burden to show that the prior art reference is not enabled and, therefore, disqualified as relevant prior art for an anticipation inquiry." *Boston Scientific Scimed, Inc. v. Cordis Corp.*, 2005 U.S. Dist. LEXIS 10751, at * 17 (D. Del. 2005). Plaintiffs have failed to introduce any proof at trial to support their contention.[13] Absent such proof, any argument by Plaintiffs on enablement regarding Bhasker must fail. *See Novo Nordisk Pharms.*, 2004 U.S. Dist. Lexis14960, at *73.

C. Claims 1 and 4 of the '318 Patent Are Obvious, And Thus, Invalid Under 35 U.S.C. § 103(a)

1. The law of obviousness

Under 35 U.S.C. § 103(a), a claimed invention is invalid as obvious if the "subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." In applying § 103, this Court is to consider: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the claimed invention and the prior art; and (4) objective indicia of non-obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007). When obviousness is based on a combination of prior art references, the Federal Circuit has made clear that "[o]bviousness does not require absolute predictability of success. . . . All that is required is a reasonable expectation of success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[T]he expectation of success need only be reasonable, not absolute" or "a guarantee").

A month before trial, the Supreme Court decided *KSR*, a landmark case that significantly "lower[s] the bar" for defendants asserting obviousness. *Seitz v. Envirotech Sys. Worldwide Inc.*,

[13] Based on Plaintiffs' claim that the flimsy two column '318 patent is somehow enabled, it is not surprising that Plaintiffs made no attempt at trial to show that Bhasker is not enabled.

2007 U.S. Dist. LEXIS 44272, at *26 (S.D. Tex. 2007) (citations omitted). The Supreme Court emphasized that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." *KSR*, 127 S. Ct. at 1746. "Innovations" that consist of combinations of elements in the prior art are to be treated with particular caution:

> Neither the enactment of § 103 nor the analysis in *Graham* disturbed this Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. For over a half-century, the Court has held that a 'patent for a combination which only unites old elements with no change in their respective functions . . . obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men.'"

Id. at 1739 (quoting *Great Atl. & Pac. Tea Co. v. Supermarket Equip.*, 340 U.S. 147,152 (1950).

The Court rejected the Federal Circuit's rigid application of the "teaching, suggestion, motivation" test in determining whether combinations of prior art references rendered patents invalid. Where the issue is obviousness based on a combination of elements in the prior art, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *KSR*, 127 S. Ct. at 1740. If a "person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* Thus, "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.*

KSR also rejected Federal Circuit precedent "that a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'" *Id.* at 1742. After *KSR*, it is clear that the "fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* For example, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *Id.*; *see also Syngenta Seeds, Inc. v. Monsanto Co.*, 2007 U.S. App. Lexis 10496, at *8 (Fed. Cir.

2007) (upholding a finding of invalidity where the prior art disclosure "plainly constitutes a suggestion" that would lead one of ordinary skill to conclude the patent at issue was obvious.).

2. Claim 1 of the '318 patent is obvious under *KSR* and its progeny

The evidence is clear and convincing that Dr. Davis did nothing more than combine the known utility of, tertiary amine, reversible CIs to treat AD with galanthamine, a tertiary amine, reversible CI with a superior therapeutic profile to physostigmine and tacrine.

a. Level Of Ordinary Skill In The Art

Defendants' evidence shows that the level of ordinary skill in the art for the '318 patent is an M.D. or Ph.D. who has sufficient knowledge and training in the area of AD, including its pathology and treatment, and knowledge of pharmacology. Levey 94:17-21; Domino 381:2-7. Plaintiffs did not present any contrary evidence. As such, Defendants' level of ordinary skill should control the inquiry.

b. Every Limitation Of Claim 1 Is Within The Scope And Content Of The Prior Art

There are two elements in Claim 1: first, a method of treating AD; second, administering to a patient a therapeutically effective amount of galanthamine. PX 1. All elements of this claim are in the prior art. First, the prior art disclosed that tertiary amine, reversible CIs like galanthamine (*i.e.*, physostigmine and tacrine) could improve higher cortical function in AD patients (*i.e.*, a method of treating AD), and second, galanthamine was a known tertiary amine, reversible CI with a superior therapeutic profile to physostigmine and tacrine, and had been shown to improve higher cortical function in patients with progressive dementia, which necessarily includes AD.

As noted in detail *supra*, in 1986 it was well known that AD was associated with a dramatic loss of acetylcholine levels in the brain, and that this loss contributed to the severity of

the symptoms of AD. Scientists sought means of increasing acetylcholine levels in AD patients to treat AD including through the use of an established class of chemical compounds known as tertiary amine CIs, in particular the tertiary amine CIs physostigmine and tacrine. By 1986, both tacrine and physostigmine had been shown to increase the levels of acetylcholine in AD patients by inhibiting the enzyme AchE and in doing so, improved cognitive function in AD patients. *See, e.g.,* Levey 178:6-179:2; Domino 382:9-383:15; PX 752 at 691 (Rathmann, 1984); PX 727 at 189-191 (C. Johns, 1983); PX 670 (K. Davis, 1983); PX 698 (Mohs, 1985); PX 699 (Mohs, 1985); PX 711 (Summers, 1981). Rathmann exemplifies the state of the art in 1985:

- "Evidence suggests that impaired cholinergic function may create learning and memory impairment . . .Therefore, primary emphasis in the treatment of Alzheimer's disease is on enhancing cholinergic function." PX 752 at 687;
- Because of the cholinergic deficit, the CIs physostigmine and tacrine were used in multiple studies to treat AD patients by inhibiting the breakdown of acetylcholine in their brains. *Id.* at 688;
- A review of six studies of physostigmine, both oral and IV infusion, showed a majority of the AD patients experienced mild to moderate or significant improvement in various aspects of "cognitive function" as measured by AD assessment scores and some patients showed clinical improvement. *Id.*;
- "Negative findings with physostigmine have been reported; however, these studies did not individualize the dose of physostigmine." *Id.*;
- "Physostigmine has limited usefulness due to its very short duration of action (<1 h) and the high incidence of peripheral cholinergic side effects. However, it has served as a useful pharmacological model;" *Id.*;
- "Results with physostigmine are encouraging and further studies with this drug prototype are needed"; *Id.*

Similarly, by 1986, the properties of galanthamine were well-known in the art. Domino 393:1-394:7; DX 58 (Cozanitis, 1974); DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977); DX 483 (Bhasker, 1974); PX 743 (Daskalov, 1980); PX 1181 (Pernov, 1961); PX 1339 (Cozanitis, 1971). In particular, galanthamine was a known reversible tertiary amine CI like physostigmine and

tacrine that had the same mechanism of action as physostigmine and tacrine, *i.e.* it would inhibit AchE in the brain. It was known that galanthamine could improve higher cortical functions. The prior art also disclosed that compared to physostigmine, galanthamine had a superior therapeutic profile. *Id.*; *see also* Levey 183:15-184:2; 189:11-190:3; 195:20-204:24; Domino 385:23-386:21; 390:10-391:15; 392:7-396:7; 402:1-18; Coyle 974:17-19; 975:3-18. Drs. Levey and Domino testified that the Daskalov, Cozanitis and/or Baraka articles exemplify the knowledge in the art in 1986 concerning galanthamine. Specifically, Daskalov (PX 743) discloses:

- Galanthamine belongs to the class of tertiary amine CIs which share the property that they have "the ability to impede acetylcholine destruction" by "inhibiting the enzyme" AchE;
- Galanthamine can be administered chronically to treat aphasia, a symptom seen in AD, without causing intolerable side effects;
- Galanthamine in doses ranging from 3-20 mg were used to treat aphasia.

Additionally, Cozanitis (DX 70) and/or Baraka (DX 71) disclose:

- Galanthamine is a centrally acting tertiary amine, reversible CI that can inhibit acetylcholinesterase in the brain, reverse scopolamine-induced amnesia, and is longer acting and has a better side-effect profile than physostigmine in clinical use.

Moreover, Drs. Levey and Domino testified that Bhasker, standing alone or in combination with the other prior art references discussed *supra*, disclose all the limitations of claim 1. Levey 205:24-223:7; 226:3-231:13; Domino 402:19-403:10; 406:18-407:25. Specifically, Bhasker discloses that galanthamine can be used to treat progressive dementias, which necessarily includes AD. DX 483

Thus, all elements of claim 1 existed in the art prior to 1986. As Dr. Levey testified, there are absolutely no differences between the scope of the prior art as reflected in Rathmann

and/or Bhasker on the one hand, and Daskalov and Cozanitis or Baraka on the other hand, and the scope of claim 1. Levey 226:3-14.

c. Motivation To Combine The Prior Art

i. *Galanthamine would have been obvious to try for AD*

A person of ordinary skill in the art would have been motivated to combine the prior art on tertiary amine, reversible CIs as a method of treating AD with the prior art on galanthamine because there was a need "to solve a problem" for which there were a "finite number of identified, predictable solutions." *KSR*, 127 S. Ct. at 1742. The problem was finding a treatment for AD that would increase acetylcholine levels in the brains of AD patients and do so in a manner that was safe and effective. Of the three known methods of raising acetylcholine levels (pre-synaptic, intra-synaptic and post-synaptic), the only one with proof of concept was the intra-synaptic or CI approach. Levey 165:17-25; 129:13-130:22; 173:13-175:13. As discussed *supra*, by 1986, there was clear evidence that the pre-synaptic approach did not treat AD, and it was questionable whether the post-synaptic approach would treat AD. PX 632 at 342 (Bartus, 1985). Under these circumstances, as in *KSR*, a person of ordinary skill in the art "has good reason to pursue the known options." *KSR*, 127 S. Ct. at 1742. The fact that tertiary amine, reversible CIs had proof of concept in treating AD and galanthamine was reported in the prior art as a tertiary amine, reversible CI that was longer-acting and had a better side-effect profile than physostigmine certainly made it obvious to try galanthamine for treating AD, rendering claim 1 obvious. Levey 165:17-25; 129:13-130:22; 173:13-175:13; 187:3-190:3.[14] *See also* DX 651 (B.

[14] Indeed, while Plaintiffs' tried to argue at trial that Dr. Bonnie Davis had a unique way of looking at the prior art that led her to her so-called "invention," Dr. Davis' statements to the PTO during the prosecution of her patent plainly show that she did not. When it came time for Dr. Davis to describe her invention to the PTO, contrary to what she said at trial, she did not say that CIs failed to treat AD or that galanthamine had a special nicotinic property that other CIs did not have that would make it ideal for AD treatment. What she said is that "useful results have been reported in some cases by treatment with physostigmine" but "its poor therapeutic index is likely to preclude its widespread use." PX 14 at 2. She then indicated that she believed that galanthamine would be effective for AD

[REDACTED]

[REDACTED]

ii. *A person of ordinary skill in the art would have been motivated to combine the prior art to use galanthamine for AD*

Beyond the fact that as of 1986 it would have been obvious to try galanthamine for AD, the prior art pointed directly to galanthamine as a treatment for AD. "This case is not one in which 'the prior art gave either no indication of which parameters were critical or no direction as to which of the many possible choices is likely to be successful,' nor is it one in which the prior art 'gave only general guidance as to the particular form of the claimed invention or how to achieve it.'" *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 2007 U.S. App. Lexis 16245, at * 56-57 (Fed. Cir. 2007) (quoting *In re Farrell*, 853 F.2d at 903). Rather, the prior art pinpointed development of tertiary amine, reversible CIs that were longer acting than physostigmine and that did not have the peripheral side-effects of physostigmine and tacrine. Levey 173:13-174:20; Domino 388:17-394:7. Dr. Bonnie Davis of course agreed saying,

[REDACTED]

because it was "being used in Europe . . . and [was] unlikely to suffer the problems of possible toxicity encountered with physostigmine." *Id.*

PX 558 at 330. In the Kendall review, on which Dr. Davis relied for her statement, it was reported that in multiple trials with physostigmine in AD patients, the drug "yielded some encouraging results" and was "an encouraging observation in an area of therapeutic uncertainty." PX 19 at 330 (Kendall, 1985); B. Davis 789:5-791:16.

The motivation to combine is confirmed by other scientists' suggestions of galanthamine as a treatment for AD. As discussed *supra*, long before Dr. Davis filed her patent application Bhasker specifically contemplated the use of galanthamine as a method of treating progressive dementias like AD. DX 483 at 45-46 (Bhasker, 1974). Dr. Domino's 1988 article, based virtually entirely on pre-1986 prior art, expressly suggested that galanthamine be used to treat AD. Domino 413:20-415:4. On the basis of his review, he came to the conclusion that galanthamine should be tried for AD. PX 756 at 295-303 (Domino, 1988); 413:20-415:4.

> At the present time the cholinergic deficiency hypothesis involving nucleus basalis and related areas in the basal forebrain of Alzheimer's patients provides the most practical means of developing new therapies. In view of the interest in experimental treatments using physostigmine and tetrahydroaminoacridine, it seems appropriate to search for other CIs (AChEI) that readily penetrate the blood-brain barrier. Galanthamine is such an agent. (PX 756 at 295).

Significantly, he did not believe there was anything inventive in having suggested galanthamine for AD. He testified he was "astonished" when he learned during the course of this litigation that Dr. Davis had a patent on galanthamine because galanthamine was an "old compound, well-known." Domino 414:1-3. As he put it, "what's new?" Domino 414:2-3. Dr. Michael Rainer reported in a medical journal in 1997 that "the notion that it may be possible to exploit the well-established central cholinergic effects of galanthamine for the treatment of AD can be traced back to the psychiatric ward at Ybbs a.d. Donau in Austria, where the first favorable case studies were reported in 1986." DX 169 at 2 (Rainer, 1997). Dr. Bonnie Davis

herself said she had great difficulty in getting galanthamine in the United States. B. Davis 811:4-12; *see also* K. Davis 1043:8-10.

d. A Person Of Ordinary Skill In The Art Would Have A Reasonable Expectation Of Success In Combining The Prior Art

Not only would a person of ordinary skill in the art have been motivated to combine the prior art on CIs with the prior art on galanthamine, there would have a reasonable expectation of success in treating AD in doing so. It is black letter law that "[t]he expectation of success need only be reasonable, not absolute" or "a guarantee". *Pfizer, Inc.*, 480 F. 3d at 1364 ("[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.").

By 1986, it had been shown that in over 10 studies in which 82 patients received either physostigmine or tacrine, the drugs improved cognitive function in 62 patients. (Smith, C., PX 1200 at 42); (Thal, PX 1205); (K. Davis PX 763 at 1422); (K. Davis, PX 670 at 451); (K. Davis, PX 727 at 189-193); (Mohs, PX 698 at 749); (Mohs, PX 699 at 28); (Summers, PX 711 at 145). Given that background, it was not only reasonable that galanthamine would produce the same or better results in treating AD than the first-generation CIs, according to Dr. Davis, it was utterly predictable: **[REDACTED]**

651; B. Davis 794:17-795:5.[15]

This case bears a striking similarity to *Imperial Chemical Industries* and *Daiichi Sankyo Co. v. Apotex, Inc.*, 2007 U.S. App. LEXIS 16576 (Fed. Cir. July 11, 2007) (unpublished)

[15] Not surprisingly, galanthamine acts exactly as predicted in AD patients. Levey 225:16-229:13. Galanthamine is a long acting CI that inhibits AChE which increases acetylcholine levels in the brain and does so without the undesirable peripheral side effects of physostigmine or tacrine. *Id.*; Levey 205:14- 205:23; Domino 393:6 – 394:7; Levey 183:15 – 184:2; 189:11 – 190:3; 195:20 – 204:25; Domino 385:23 – 386:21; 390:10 – 391:15; 392:7 – 394:16; -- 402:1 – 402:18; Coyle 974:17 – 974:19; 975:3 – 975:17; Domino 393:1 – 394:6; DX 58 (Cozanitis, 1974); DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977); DX 483 (Bhasker, 1974); PX 743 (Daskalov, 1980); PX 1181 (Pernov, 1961); PX 1339 (Cozanitis, 1971).

(attached hereto as an Exhibit). In *ICI*, for all the same reasons applicable here, this Court held that a patent claim directed to a method of treating hypertension with a compound that belonged to a class of compounds known to treat hypertension was invalid as obvious. *Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 777 F. Supp. 330, 373 (D. Del. 1991). As here, the inventors did not do any testing on the compound, atenolol, for its use in treating hypertension. Noting that "[t]he prior art teaches the way in which this class of compounds functions and the uses for this class of compounds," the Court held that the patent was invalid. *Id.* at 347.

Likewise, in *Daiichi*, the patent claimed "a method for treating bacterial infections by topically administering the antibiotic ofloxacin into the ear." 2007 U.S. App. LEXIS 16576, at *2. The Federal Circuit held the method of treatment claim obvious since a prior art reference "taught the successful use of ear drops" using a compound that was in the same family as the claimed compound. *Id.* at *8-12. Since ciprofloxacin was known to be safe and effective, the court concluded that "[o]ne would understand that a very close relative to Ciprofloxacin was safe and effective in treatment of middle ear disease, otitis media." *Id.* at * 9-10.

Similarly, claim 1 is invalid because Dr. Davis has done nothing more than claim a method of treating AD with a tertiary amine CI, a class of compounds that had been shown to work for the treatment of AD. The mere use of another well-tolerated tertiary amine CI to treat AD is not the type of innovation that the patent law recognizes. Dr. Davis took known elements from the prior art and combined them in an entirely expected fashion. *KSR* makes clear that Plaintiffs should not be permitted to withdraw galanthamine into the field of their monopoly.

3. Claim 4 Of The '318 Patent Is Obvious

For all the same reasons that claim 1 is obvious, claim 4 is obvious. Additionally, the evidence shows that the prior art disclosed that galanthamine can be administered orally and in

dosage ranges that fall within the range of 10-2000 mg and were shown to have cognitive-enhancing effects at such doses. PX 743 (Daskalov, 1980). In particular, Daskalov discloses:

- Galanthamine can be administered orally in doses ranging from 3-20 mg long-term to treat aphasia, a symptom seen in AD, without causing intolerable side effects.

Moreover, it would have been a matter of routine experimentation in 1986, as testified to by Plaintiffs' experts, to find a dose within the range that was therapeutically effective for treating AD. Raskind 1178:12-1179:15. Accordingly, claim 4 is obvious.

4. Plaintiffs' Non-Obviousness Arguments Fail

Faced with the clear fact that the elements of the claimed invention were in the prior art, Plaintiffs and their experts argued that the art taught away from the use of CIs as treatments for AD by selectively quoting the art, that scientists were pursuing other treatments for AD, an irrelevant fact, and incredibly that the properties of galanthamine were not suitable for treatment of AD.

a. Plaintiffs Cannot Escape The Prior Art Showing That CIs Improved Cognitive Function In AD Patients.

Plaintiffs selectively present comments from a handful of articles in an attempt to show that CIs were not successful. The Federal Circuit rejected an identical approach in *ICI*, 777 F. Supp. at 368-71, *aff'd* 972 F.2d 1354 (Fed. Cir. 1992). The court noted that while there may have been "papers which did not show dramatic results in the reduction of blood pressure with the use of a beta-blocker," as the plaintiff had argued, it did not "alter the fact that the prior art patents and literature would create the expectation that a beta-blocker compound, such as atenolol, would have anti-hypertensive utility." *Id.* at 369. Thus, the court found the patent invalid for obviousness. *Id.* at 373. Here, the fact that physostigmine did not produce "dramatic results" in all studies or that, after the '318 patent application was filed, tacrine proved to have side effects that limited its use does not undermine the obviousness of the invention here.

In any event, the few negative studies Plaintiffs cite were not due to the failure of the drugs, but to poor study design or were mischaracterized by Plaintiffs. PX 727 at 189-193 (C. John, 1983). The C. Johns, *et al.* review concluded that studies in which physostigmine and tacrine failed to show improved cognitive functioning in AD patients were poorly designed: "The apparently contradictory nature of some findings may be explained and reconciled by careful review of appropriate study design and patient selection." PX 727 at 189. The Mohs et al. article (PX 698) relied upon by Dr. Raskind[16] to show that "memory actually slightly declined in physostigmine compared to placebo" actually showed that for all but one patient memory was improved. Raskind 1230:4 – 1231:2 ("the slight worsening on memory items was largely attributable to one patient (3) whose memory subscale score was five points higher on physostigmine than placebo."). Dr. Raskind also failed to inform the Court that the study reported that physostigmine produced "improvement in both cognitive and noncognitive areas" in 7 of the 10 patients in the study. PX 698 at 734-735.

Significantly, in the pharmaceutical arts, no drug produces improvement in every AD patient and frequently drugs do not cure disease. Razadyne[17] does not produce improvement in every patient. Levey 109:2-6. Nor has any cure for AD been found yet. Domino 423:15-16. However, the reality is that by 1986, there is overwhelming evidence that in properly designed studies, patients with AD experienced improved cognitive function after taking physostigmine and/or tacrine. PX 19 at 330-36 (Kendall, 1985); PX 670 (K. Davis, 1983); PX 698 (Mohs, 1985); PX 699 (Mohs, 1985); PX 711 (Summers, 1981); PX 727 (C. Johns, 1983); PX 752 (Rathmann, 1984); PX 763 (K. Davis, 1982); PX 1148 (Greenwald, 1983); PX 1200 (Smith,

[16] Unlike Defendants' experts who are not personally financially benefiting from their participation in this case, Dr. Raskind is a paid consultant in this case and has been a paid consultant for Plaintiffs on galanthamine for many years. Raskind 1195:21-1196:6.

[17] "Plaintiffs have sold galanthamine under the trade names Razadyne and Reminyl. For ease of reference and consistency, Defendants simply refer throughout this brief to Razadyne, although some of the cited documents may use the term Reminyl."

1979); PX 1205 (Thal, 1979); DX 1233 (Timeline of prior art); Coyle 911:21-912:6; 971:21-972:1; Raskind 1250:7-1251:16.

b. Work with other treatments for AD did not teach away from the use of CIs

At trial, Plaintiffs focused on presenting evidence that scientists pursued treatments of AD other than CIs, particularly the muscarinic agonist approach, in an attempt to establish that persons of skill had given up on CIs by 1986.[18] The fact that some scientists considered other approaches for treating AD is not inconsistent with the continued pursuit of CIs. Despite the success of the first generation CIs in establishing that CIs could improve cognitive function through increases in acetylcholine levels, nobody viewed CIs as a panacea. Levey 150:12-152:8. CIs, including Razadyne, do not cure AD and at best have a modest effect on the course of the disease. *Id.* 150:8-16. For this reason, scientists always have pursued other approaches in hopes of finding a more effective treatment or even a cure for AD. *Id.* 299:20-300:11.[19]

The interest in CIs as viable treatments for AD continued long after 1986. In 1987, Drs. Bonnie and Ken Davis among others concluded that "a subgroup of [AD] patients may derive meaningful benefit from oral physostigmine treatment" and "that physostigmine does produce a meaningful reduction in symptom severity in at least some patients with Alzheimer's Disease." 743:3-4; DX 652 at 73 (Hollander, 1987). In 1988, an international symposium of the world's experts in Alzheimer's therapy convened to "focus on one of the most promising approaches, the use of cholinesterase inhibitors, to elevate acetylcholine levels in the brain" (DX 658), which would not have occurred if CIs were viewed as a research dead-end. That same year, Dr.

[18] Plaintiffs' cross examination of defense expert Levey, for instance, consisted almost entirely of questions concerning the muscarinic agonist approach to AD treatments rather than to his testimony concerning the cholinergic hypothesis and pre-1986 studies with tertiary CIs. Levey 294:7-307:14.

[19] In much the same way, scientists continue to pursue new ideas for treatments of cancer. Chemotherapy, for instance, is a treatment for cancer that has success in some instances. Nonetheless, because it is not a cure for the disease in all instances, scientists continue to pursue other approaches as well.

Domino published his article specifically suggesting that galanthamine, a CI, be considered as an AD treatment. PX 756 (Domino, 1988).

Plaintiffs' own demonstrative showing the treatment approaches for AD over the years substantiates this point. PX 1401a. Of all the approaches to AD tried over the years, CIs have been the most prevalent. PX 1401a; *see also* PX 633 at 190-192 (Giacobini, 1996). By 1996, there were at least 14 CIs other than tacrine and physostigmine in clinical trials, demonstrating that pharmaceutical companies were sufficiently encouraged to spend hundreds of millions of dollars in development of the drugs. PX 1401a. Given the normal ten year path from laboratory testing to clinical trials, the pursuit of these drugs began in 1986, at the same time that Dr. Davis filed her patent application. PX 663 at 190-192 (Giacobini, 1996); (Domino 441:14-442:1).

c. Galanthamine's properties did not teach away from its use as a treatment for AD

Finally, Plaintiffs make the absurd argument that galanthamine's properties would have led a person of skill in the art away from using it for AD.[20] Plaintiffs' main evidence was a misleading chart presented by Dr. Coyle, that Plaintiffs ultimately did not want to introduce into evidence. The chart purported to present various characteristics of galanthamine that would be relevant to the consideration of whether to use the drug for the treatment of AD. Not surprisingly, the chart excluded the factors that the [21]prior art in 1986 specifically listed as desirable for the next generation of CIs: fewer muscarinic peripheral side-effects, action in the brain, and greater safety and tolerability. Coyle 973:6-974:7. When confronted with this omission, Dr. Coyle admitted that galanthamine "was known to have minimal side-effects"

[20] This is yet another place where Plaintiffs take wholly inconsistent positions. To defeat obviousness, Plaintiffs argue that one of skill in the art would have been led away from galanthamine by its properties which is entirely inconsistent with their argument that galanthamine was enabled by the disclosure of the patent.

[21] Dr. Coyle testified that he has been friends with Drs. Bonnie and Ken Davis for over thirty-years and has been a paid consultant (including in this case) for galanthamine for the Drs. Davis for over 20 years. Coyle 972:2-25.

(Coyle: 974:20-23), had less side-effects than physostigmine which was desirable (Coyle: 910:11-24), had some central nervous system effects[22], and was reported to be safe and tolerable. Coyle 973:25-974:7; 980:24-981:1. Galanthamine thus satisfied the very criteria that the prior art targeted as desirable in the next generation of CIs.

D. Plaintiffs Have Provided No Persuasive, Reliable Evidence of Secondary Considerations of Non-Obviousness to Rebut the Finding of Obviousness

Plaintiffs spent considerable time presenting a number of secondary considerations in hopes of rebutting the prima facie showing of obviousness. Plaintiffs' evidence, however, does not meet the requirements of secondary considerations and in any event does not overcome the strong showing that the use of galanthamine as a method of treating AD was obvious based on the prior art.

1. The Law Regarding Secondary Considerations

When a court reaches the conclusion that an asserted claim is prima facie obvious, the patentee may attempt to present objective secondary considerations of nonobviousness. *WMS Gaming Inc. v. Int'l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999). In the context of secondary considerations, "'argument' and 'conjecture' are insufficient." *Demaco Corp.v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1393 (Fed. Cir. 1988) (citing *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1546 (Fed. Cir. 1984)). A patentee must establish a nexus between the evidence presented and the merits of the claimed invention, *i.e.*, the patentee bears the burden of demonstrating "a legally and factually sufficient connection" between the evidence and the patented invention to demonstrate that the evidence offered does, in fact, corroborate the invention's nonobviousness. *In re Paulson*, 30 F.3d 1475, 1482 (Fed. Cir. 1994);

[22] While Dr. Coyle said only that galanthamine had some central effects, Defendants introduced six prior art references that disclosed that galanthamine had central effects and/or was used to treat disturbances of higher cortical functioning similar to the disturbances seen in AD patients. DX 58 (Cozanitis, 1974); DX 70 (Cozanitis, 1977); DX 71 (Baraka, 1977); DX 484 (Bhasker, 1974); PX 743 (Daskalov, 1980); PX 744 (Luria, 1969).

see also In re GPAC Inc., 57 F.3d 1573, 1580 (Fed. Cir. 1995). Even when present, however, the evidence of secondary considerations still must be of sufficient weight to override a determination of obviousness based on primary considerations where there is strong evidence of obviousness. *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991).

2. Plaintiffs Have Not Established that There Are Unexpected Benefits Associated with Galanthamine

Plaintiffs assert as secondary considerations two purported "unexpected benefits" of galanthamine. To succeed, Plaintiffs must prove that the benefits claimed to be unexpected *actually* occur. *See In re DeBlauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984). Indeed, speculation or unproven hypotheses about what might become an "unexpected benefit" simply is not enough: "[I]t is well settled that unexpected results ***must be established by factual evidence***. 'Mere argument or conclusory statements . . . does not suffice.'" *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) (quoting *In re DeBlauwe*, 736 F.2d at 705) (emphasis added). Thus, an applicant cannot prove unexpected benefits with "bare statements without objective evidentiary support." *CFMT, Inc. v. YieldUp Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003).

a. Nicotinic allosteric modulator

Plaintiffs argue that galanthamine's action as a nicotinic allosteric modulator provided an unexpected benefit in treating AD with galanthamine. However, Plaintiffs' own expert, Dr. Raskind, could not testify that there was any benefit attributable to the fact that galanthamine is a nicotinic allosteric modulator. Raskind 1219:9-21.

[REDACTED]

[REDACTED]

b. Slowed Progression of AD

Plaintiffs also claim that galanthamine unexpectedly slows or treats AD, as opposed to just treating the symptoms of the disease. Again, Plaintiffs have no proof. Janssen's own prescribing information ("PI") for Razadyne states: "There is no evidence that galanthamine alters the course of the underlying dementing process." DX 655 at 1. Dr. Levey agreed. 243:19-244:4. The best that Plaintiffs' expert Dr. Coyle could say is that it is "possible" that galanthamine slows the disease course, but even so, that such possibility would apply equally to other CIs. 932:5-9; 933:16-21. Under *In re Geisler* and *In re DeBlauwe*, Plaintiffs' sheer speculation is not sufficient to meet their burden.

3. Plaintiffs Have Not Established that Galanthamine Was Met with Skepticism

Plaintiffs argue that Dr. Davis was met with skepticism when she attempted to license galanthamine. But a failure to license is not tantamount to an expression of skepticism. As Dr. Davis stated, the pharmaceutical companies she approached had many reasons for choosing whether or not to license a patent: that the companies may have their own research programs in

place; concern whether the drug will make sufficient profit in the marketplace; the nature/position of the patent protection; availability of raw material; and lack of FDA approval, among others. B. Davis 805:23-812:22. The fact that some companies turned down her request to license the patent is not indicative of skepticism about galanthamine's use as a treatment for AD. In fact, despite only sporadically approaching companies with offers of licenses, Dr. Davis licensed the patent three separate times in a five year period. B. Davis 819:15-823:7.

4. Razadyne Is Not a Commercial Success

Defendants' commercial success expert, Harry Boghigian, demonstrated at trial that Razadyne is not a commercial success. First, Razadyne fails the most basic test of commercial success – Based on his analysis of the sales of Razadyne and the various costs associated therewith, Boghigian determined that Razadyne has resulted in a

[REDACTED]

In situations where a product merely has the showing of commercial

[REDACTED]

success is weak. *Medpointe Healthcare Inc. v. Hi-Tech Pharmacal Co.*,115 Fed. Appx. 76, 80-81 (Fed. Cir. 2004) (finding that commercial success evidence is considered "weak" and "tenuous" where the product has only [redacted] in the amount of money made, with the long-term profitability yet to be established).

Second, Razadyne is not even in the [redacted]

Plaintiffs also have failed to establish that Razadyne's sales have the required nexus to the features of the claimed invention. [redacted] Commercial success is irrelevant unless it

[redacted]

is a "direct result of the unique characteristics of the claimed invention – as opposed to other economic and commercial factors." *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996); *see also McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003) ("[A] massive marketing and advertising campaign ... obscur[es] any nexus that might have existed between the merits of the product and its commercial success.").

[REDACTED]

Despite these and other marketing efforts,[29] Razadyne's sales revenue

[REDACTED]

In sum, Razadyne has not enjoyed the kind of "commercial success" that would overcome the strong showing of obviousness in this case. *Leapfrog Enterps., Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

E. Claims 1 and 4 Are Invalid For Lack of Enablement

Plaintiffs cannot win on both the enablement and obviousness defenses given the minimal disclosure of the patent. The patent law requires that the inventor enable those of skill in the art to use claimed invention. 35 U.S.C. § 112. If Plaintiffs are correct that the prior art did not provide a reasonable expectation that galanthamine would work to treat AD, then the minimal disclosure of the patent is not sufficient for enablement.

1. The Law of Enablement

[29] [REDACTED]

Enablement requires disclosure of a "practical utility for the invention," as of the date of the invention. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999); *see Curtiss-Wright Corp. v. Link Aviation, Inc.*, 182 F. Supp. 106, 123 (N.D.N.Y. 1959) ("Utility must be determined as of the date of the invention. Present day requirements due to scientific advancement is not the test."). "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997); *see also LP Matthews LLC v. Bath & Body Works, Inc.*, 458 F. Supp. 2d 198, 209 (D. Del. 2006)(quoting *Genentech, Inc.*, 108 F.3d at 1366). Thus, a specification which provides "only a starting point, a direction for further research" does not provide an enabling disclosure. *Genentech, Inc.*, 108 F.3d at 1366.

The Federal Circuit specifically has addressed enablement in the context of pharmaceutical method of treatment patents. In *Rasmusson v. SmithKline Beecham Corp.*, the Federal Circuit reiterated the long-held principle that the patent can be invalid "under either section 112, paragraph 1 for lack of enablement, or 'section 101 for lack of utility when there is a complete absence of data supporting the statements which set forth the desired results of the claimed invention.'" 413 F.3d 1318, 1323 (Fed. Cir. 2005) (quoting *In re Cortright*, 165 F.3d at 1356 (internal quotation omitted)).

In *Rasmusson*, the applicant had provided no experimental data in support of his claimed method for treating prostate cancer with a chemical compound called finasteride. In upholding the Board's determination that the patent application at issue was not enabled, the Court held:

> [W]here there is no indication that one skilled in [the] art ***would accept without question*** statements [as to the effects of the claimed drug products] and ***no evidence*** has been presented to demonstrate that the claimed products have those effects, an applicant has failed to demonstrate sufficient utility and therefore cannot establish enablement.

413 F.3d at 1323 (internal quotation omitted)(alteration in original)(emphasis added). In such a situation, the Court held that "substantiating evidence" is necessary "unless one with ordinary skill in the art would ***accept the allegations as obviously correct***" as of the time the patent application was filed. *Id.* (quotation omitted) (emphasis added).

The Court rejected Rasmusson's assertion that the enablement requirement of § 112 requires only that the intended use of the patent is "not implausible:"

> If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention ***rather than merely proposing an unproved hypothesis.***

Id. at 1325 (emphasis added).

2. Claims 1 and 4 of the '318 Patent are Invalid for Lack of Enablement Under the Federal Circuit's Decision in *Rasmusson v. SmithKline Beecham Corp.*

a. The '318 Patent's Disclosures Do Not Meet The Requirements Of *Rasmusson*

As interpreted by Plaintiffs, the prior art provides no basis for believing that galanthamine would work as a treatment for AD. If Plaintiffs are correct that the prior art does not establish a reasonable expectation that galanthamine would work as a treatment for AD, and therefore the patent is not obvious, then persons of ordinary skill in the art could not have believed "without question" that galanthamine would treat AD.

Plaintiffs vehemently asserted throughout the prosecution of the patent and in this case that based on the prior art no one would have believed that galanthamine would work as a treatment of AD. Dr. Bonnie Davis told the PTO that the prior art provided no basis to believe that galanthamine would have utility as a treatment for AD. PX 14 at 3, 6 ("One cannot predict with any degree of confidence what the effect of any given chemical on a particular brain

function or brain condition may be." "Nothing in this teaching leads to an expectation of utility against Alzheimer's disease."). Plaintiffs' experts made similar arguments in this litigation. Dr. Coyle, when asked if he would accept "without question" Dr. Davis' claim that galanthamine treats AD, answered that he would not:

> Q. All right. So would one of ordinary skill in 1986, knowing everything that you've said today about the cholinesterase inhibitor approach, tacrine, physostigmine, what-have-you, would one of ordinary skill, the nicotinic receptors, the muscarinic receptors -- would one of ordinary skill in the art in 1986 have accepted, without question, that galanthamine could be used to treat Alzheimer's?
> A. That is -- I would say without question. I would -- **no, I wouldn't say without question. I would want some additional information. What does it do? How does it work? You know, appropriate models.**

Coyle 993:8-994:2 (emphasis added). Likewise, Dr. Raskind admitted that a person of skill in the art would not have accepted that galanthamine would work to treat AD "without question":

> Q. You would not accept without question, based on what's disclosed [in the patent], that galanthamine would treat Alzheimer's disease; correct?
> A. Well, it could be used, but you wouldn't know whether it was effective.
> Q. Because there's -- Dr. Davis provided absolutely no information in this patent to show that galanthamine, in fact, did improve cognition in Alzheimer's disease patients; right?
> A. That's correct.

Raskind 1269:23-1270:17.

Thus, Plaintiffs' adamant position is that in 1986 no one would have known that galanthamine would work. At most, Dr. Davis merely had a proposal that "raised very interesting questions" and then left it to others to figure out the answers. Coyle 980:14-20.

Raskind 1269:23-1270:17.

Thus, Plaintiffs' adamant position is that in 1986 no one would have known that galanthamine would work. At most, Dr. Davis merely had a proposal that "raised very interesting questions" and then left it to others to figure out the answers. Coyle 980:14-20.

b. The Patent Provides No Credible Evidence Of Utility Beyond that Was Already In The Prior Art

Nor does the patent meet the other prong of the *Rasmussen* analysis because it does not provide any evidence supporting the utility of galanthamine as a treatment for AD. The patent consists of only two columns that do nothing more than provide the same information that was available in the prior art and that, according to Plaintiffs' experts, was not sufficient to establish a reasonable expectation that galanthamine would work as a treatment for AD. Plaintiffs point to only two portions of the patent that they contend provide the disclosure necessary to enablement.

First, Plaintiffs point to lines 11-33 of Column 1. This excerpt states in its entirety:

> Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in Anaesthesia 29 163-8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in Acta Anseth. Scand. 24:166-168 (1980) describe the effect of galanthamine on plasma ACTH values during anaethesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.
>
> Il'yuchenok et al (Chemical Abstracts 70 36296K describe the appearance of Θ-rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.
>
> Increase in short-term memory in dogs by use of galanthamine is described by Kraus in Chemical Abstracts 81 72615Z.
>
> The antagonistic effect of galanthamine to scopolamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in Zhurnal Vysshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA) 26:1091-1093, 1976.

These five "disclosures" provide no information beyond what is in the prior art. In fact, the disclosures are expressly from the prior art: first, that galanthamine is a CI (PX 1 at 1:11-13); second, that Cozanitis in two studies showed an increase in cortisol and acetylcholine in plasma when galanthamine was administered together with atropine (*Id.* at 1:13-21); third, that administration of galanthamine to rabbits intravenously caused the appearance of brain waves (*Id.* at 1:22-25); fourth, that the short-term memory of dogs was improved with the

administration of galanthamine (*Id.* at 1:26-28); and fifth, that galanthamine has an antagonistic effect on the scopolamine-induced amnesia in rats (*Id.* at 1: 29-33).

Each disclosure is merely a citation to the prior art, rather than a new insight made by Dr. Davis or results of testing supporting the theory that galanthamine could be useful for treating AD. None of the disclosures provides any reason to believe that galanthamine will succeed as a treatment for AD beyond what is already disclosed in the prior art. In short, this disclosure of well-established, non-controversial propositions is not sufficient to enable the patent.

Plaintiffs also have argued that the patent is enabled because it discloses an animal model at column 2, lines 45-50. But the patent discloses only an animal model that potentially could be used to demonstrate the effectiveness of galanthamine as a treatment for AD, but in fact had not yet been used. Dr. Davis had not tested galanthamine in the model and therefore provided no data supporting the utility of galanthamine. As Dr. Coyle aptly put it: "[Dr. Davis] had a proposal that connected the dots that raised very interesting questions and worth the effort to check it out in a model in which there is degeneration of cholinergic neurons in [which] both nicotinic and muscarinic receptors would come into play." Coyle 980:16-20. In fact, Dr. Davis testified that at the time she submitted the patent application, she had no idea if galanthamine, a CI, would work. B. Davis 712:14-19. A research plan that is to be executed in the future is not sufficient to establish enablement. *Northpoint Tech., Ltd. v. MDS Am., Inc.*, 413 F.3d 1301, 1310 (Fed. Cir. 2005) (There is no "enablement when 'the teachings set forth in the specifications provide no more than a plan or invitation for those of skill in the art to experiment.'"(quoting *Enzo Biochem, Inc. v. Calgene Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999) (internal quotation omitted))); *see also Fiers v. Revel*, 984 F.2d 1164, 1169 (Fed. Cir. 1993) ("[T]he policy of the statute . . . is to promote disclosure of inventions, not of research plans.").

c. Plaintiffs' Nicotinic Receptor Theory

After the Court commented on how little information was in the patent[30], Plaintiffs presented Dr. Raskind to opine that the patent disclosed a nicotinic receptor theory that would have been recognized by one of ordinary skill in the art as proof of utility. Raskind 1180:2-1184:17.

Plaintiffs' belated assertion of the nicotinic receptor theory of enablement suffers from two fatal defects. First, Plaintiffs have not presented properly any expert opinion concerning the nicotinic receptor theory. The only Plaintiffs' expert who testified that the nicotinic receptor theory is disclosed in the patent and would have made one of ordinary skill in the art believe that galanthamine would work as a treatment of AD was Dr. Raskind. Most importantly, Dr. Raskind's opinion concerning the nicotinic receptor theory and enablement was never disclosed in his expert report. Raskind 1198:9-1200:10 The sum total of his expert disclosure concerning enablement is as follows:

[REDACTED]

Raskind 1198:9-11; 1199:9-17.

There is no mention whatsoever of the nicotinic receptor theory in Dr. Raskind's expert report or in any of the prior art in Column 1 of the patent that even claims to disclose the theory. The rules of this Court make very clear that a litigant cannot introduce expert testimony at trial that has not been disclosed in an expert report.[31]

[30] The Court stated: "[B]ut I have to say that when I look at the mountain of information that you've given me and I look at the facts that the patent says very little other than use, try, galanthamine, it leaves me – I feel like there's something missing." 1149:2-6.

[31] Defendants request that the Court strike Dr. Raskind's testimony on enablement due to Plaintiffs' violation of this rule. A new trial would be highly prejudicial to Defendants and financially beneficial to Plaintiffs. The '318

This is precisely the circumstance that the rule is intended to address. Plaintiffs gave no notice in the expert report that they would be presenting expert testimony that the patent is in fact enabled due to the disclosure of the nicotinic receptor theory, but rather sandbagged Defendants mid-way through trial. Dr. Raskind's testimony clearly exceeds the scope of his report and should be stricken. Plaintiffs have no other expert testimony responding to the enablement defense. This is sufficient to find for Defendants on the enablement defense.[32]

Second, the nicotinic receptor theory is an *ex post facto* attempt to save the patent that is not supported by the patent, the record in the case, or common sense. The patent does not discuss nicotinic receptors, their role in AD, or the effectiveness of a CI that could bind to them. The patent, therefore, does not disclose the theory to persons of ordinary skill in the art.

In fact, Dr. Davis never articulated the nicotinic receptor theory at any time prior to this litigation. Dr. Davis never mentioned the nicotinic receptor theory in her filings with the PTO. PX 14. Dr. Davis did not publish articles articulating the nicotinic receptor theory and, in her letters to potential licensees explaining the rationale for galanthamine as a treatment for AD, she never mentioned the so-called unique galanthamine nicotinic receptor theory. DX 651 (B. Davis); DX 652 (B. Davis, 1987); PX 698 (Mohs, 1985); PX 699 (Mohs, 1985). For example, in a document she wrote titled, "Galanthamine for Alzheimer's Disease," which Dr. Davis sent to potential licensing partners, she devotes five single-spaced pages describing why galanthamine should be used for AD without once mentioning nicotinic receptors. DX 651 (B. Davis); B. Davis 794:1-8. What she does tout in her letters is precisely the point made by Defendants'

patent expires in December 2008 and therefore Defendants need to have this case resolved as quickly as possible to reap any benefits from filing ANDAs on this drug.

[32] While Dr. Davis provided testimony at trial concerning the nicotinic system, she was not an expert in this case and did not provide the necessary opinions on enablement. Interestingly, Dr. Davis' testimony concerning the nicotinic system provided information far beyond what appeared in the patent or what she has said at any time in the past. B. Davis 791:17-804:14. Dr Coyle also mentioned the nicotinic receptor theory, but did not provide an expert opinion on enablement on that theory.

experts concerning the prior art:

[REDACTED]

is simply inconceivable that Dr. Davis had a groundbreaking "insight" about galanthamine's unique effect on the nicotinic system and its alleged importance to treating AD, yet can produce no writing in which it is memorialized,[33] and would not have touted it when attempting to convince others to invest in her "invention." On the contrary, her writings show that it was completely expected that "cholinesterase inhibitors would be expected to have nicotinic effects." PX 324.

Additionally, even if Dr. Davis' insight was that the nicotinic receptors were important for AD, Plaintiffs' own experts testified that no one was looking at the nicotinic receptors and no one even knew if they were important to AD as of 1986. For example, Dr. Coyle said that "it was very unclear what nicotinic receptors were doing in the brain" and researchers did not "see any effect" of "nicotinic stimulation in the brain" and that those results would "not encourage one to pursue" that type of drug (like galanthamine). Coyle 870:20-872:13; PX 632.

In sum, Plaintiffs provided no credible evidence that the nicotinic receptor theory establishes enablement.

3. Claim 4 Is Not Enabled

For all the same reasons that claim 1 is not enabled, claim 4 is not enabled.

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[33] In her redirect testimony, Dr. Davis was shown a letter she wrote in February 1989, three years after she filed her patent application as support for the nicotinic receptor theory. PX 1061. The reference does not articulate a theory that galanthamine is more useful because it binds to the nicotinic receptors. Rather the reference to nicotinic receptors in its entirety states:

[REDACTED]

sentence relates solely to Dr. Davis' evaluation of scopolamine dementia and does not articulate a theory that galanthamine's reaction with nicotinic receptors is the key to her invention.

In cases involving unpredictable factors, including the chemical arts, the Federal Circuit has "refused to find broad generic claims enabled by specifications that demonstrate the enablement of only one or a few embodiments and do not demonstrate with reasonable specificity how to make and use other potential embodiments across the full scope of the claim." *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996); see also *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) ("In cases involving unpredictable factors such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.").

The '318 patent contains no information to support the conclusion that the entire dosage range of 10 to 2000 mg is therapeutically effective, as required by the claims. Moreover, the undisputed evidence at trial was that no one would administer dosages of galanthamine over the full scope of the range. Domino 408:23 – 412:10; PX 1215 (The Merck Index). Dr. Domino pointed out that a large portion of doses encompassed by Claim 4 would likely to kill a patient. 411:11-21.

Under factually similar circumstances, a court held that a pharmaceutical patent with an exceedingly broad dose range disclosure, combined with no data offered in support of such a broad disclosure, or guidance on how to practice the claimed invention, does not meet the requirement of an adequate disclosure required by 35 U.S.C. § 112. *See ICI*, 777 F. Supp. at 373-75 (holding that a method patent on atenolol, with a dose range disclosure of 25-1200 mg, was not enabled due to the breadth of the range, the lack of data supporting efficacy in the entire range, and the act that several years of dose studies had to be conducted with atenolol to determine its ultimately, much lower, effective range).

One of ordinary skill in the art, as of 1986 or today, would not have been able to practice the entire scope of Claim 4 because the vast majority of the doses in the dosage range disclosed Claim 4 are inefficacious and/or intolerable in humans. Consequently, Claim 4 of the '318 patent is not enabled, and thus, invalid.

IV. CONCLUSION

Defendants have presented clear and convincing evidence that the '318 patent is invalid. Particularly given *KSR*, using galanthamine to treat AD was anticipated by Bhasker and/or obvious based on the prior art. If, however, the Court finds that her invention was not obvious or anticipated, the patent is not enabled as Dr. Davis provided no data that her invention would work and those of ordinary skill would not accept without question that one could use galanthamine to treat AD.

Respectfully submitted,

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